

### ***Remarks***

Applicant has carefully considered this Application in connection with the Examiner's Action, and respectfully request reconsideration of this Application in view of the foregoing amendment, and the following remarks.

Claims 1 – 6 and 8 were previously cancelled and claims 9 – 13 were previously added by preliminary amendment. Accordingly, Claims 7, 9 – 13 are presently pending in the Application, with Claim 7 being the independent claim.

#### ***I. Rejection of Claims 1-3 under 35 U.S.C. § 103(a)***

Claims 7 and 9 – 13 are rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Volosov et al (WO 00/01416) and Benes et al (EP 751129), in view of Simpson et al (Trends in Pharm Sciences, 1999). For the reasons discussed below, Applicant respectfully traverses the rejection.

The Examiner cites Volosov for teaching compounds of Formula I, wherein R1 and R2 represent an oxo group take together, and where R1 represents H and R2 represents OH, and their use as anti-epileptic drugs.

The Examiner cites Benes for teaching compounds of Formula I, wherein R1 represents H and R2 represents acetoxo, and that such compounds serve as effective agents in treating epilepsy.

The Examiner cites Simpson for teaching that tinnitus is a form of "sensory epilepsy", as well as the proposition that anticonvulsants could be useful for the treatment of tinnitus. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the drugs taught by Volosov and Benes and administered them for the treatment of tinnitus. Applicant respectfully disagrees with the Examiner's conclusion.

Applicant has found that the compound of Formula I, recited at Claim 7, in free base or acid addition salt form is useful in the prevention and treatment of tinnitus. The references cited by the Examiner, singularly or in combination, do not teach or suggest Applicant's invention as expressly taught by Claims 7 and 9 – 13. Furthermore, a person of ordinary skill in the art at the time of the invention would not have been led to the references in a manner suggested by the Examiner.

Volosov teaches controlled delivery and sustained release of an active ingredient and an excipient, wherein the excipient is characterized by low melting. Specifically, Volosov teaches the combination of an active agent and a low-melting wax, such as glycerides of long chain fatty acids. (See Volosov, pages 1 – 3.) Volosov is useful for administering a lesser amount of drug than required by conventional methods and loading more drug in smaller dispensing systems. (See Volosov, page 3.) The Examiner asserts that Volosov teaches oxcarbazepine (OXC) and 10-hydroxycarbazepine (MHD) for the treatment of epilepsy.

Applicant, however, asserts that OXC and MHD are merely taught as model compounds for testing Volosov's controlled release system using low-melting wax. For instance, Volosov discusses OXC and MHD being ideal model compounds because optimization of delivery in the GI tract is desirable for both compounds. (See Volosov, page 5.) Moreover, there is no discussion or teaching whatsoever in Volosov for treating tinnitus or the underlying biochemical mechanism for tinnitus, or epilepsy for that matter. Epilepsy is merely mentioned in the general descriptive narrative of the model compounds used for testing controlled release in Volosov's low-melting wax delivery system. (See Volosov, Background section at page 5.)

Thus, contrary to the statement of the Examiner, Volosov does not teach Applicant's invention because Volosov fails to teach compounds of Formula I wherein R1 is H and R2 is an alkyl carbonyloxy for the treatment of tinnitus, as expressly required by Applicant's Claim 7.

The Examiner also cites Benes, in combination with Volosov. Benes, however, fails to teach compounds of Formula I, wherein R1 and R2 together form an oxo group and wherein R1 is a H and R2 is a hydroxy, useful for the treatment of tinnitus. Benes, rather, teaches substituted carbamazepine to overcome problems faced by MHD in the treatment of epilepsy. Benes explains that MHD is not used in practice because its preferred route is hampered by its low bioavailability and short half-life. (See Benes, Detailed Description) Also, the many different enantiomers formed during metabolism, and patient-specific results, make MHD unsuccessful for treating epilepsy. (See Benes, Detailed Description) Thus, while Benes is useful for teaching an improved formulation of MHD for the treatment of seizures, nowhere does Benes discuss or teach tinnitus or

compounds of Formula 1 for the treatment of tinnitus as expressly taught by Applicant's Claim 7.

The Examiner has cited Simpson as the motivation for combining Volosov and Benes, however Simpson not only fails to bridge the gap between the cited references and Applicant's invention, Simpson fails to lead one skilled in the art to arrive at Applicant's invention.

Simpson specifically states that there is no widely accepted affective treatment for tinnitus. (See Simpson, page 12) Moreover, Simpson teaches that numerous conditions can be linked to the occurrence of tinnitus; thereby supporting the theory that tinnitus could be the result of a number of pathological processes. (See Simpson, pages 12 & 14)

Simpson teaches that the standard treatment for tinnitus is lignocaine or, in some instances, treatment with anti-depressants. (See Simpson, pages 12 & 14) While the Examiner cites Simpson for teaching anticonvulsants as a suitable treatment for tinnitus, Simpson actually teaches that anticonvulsants are often accompanied by troublesome side-effects, and the initial effectiveness is often short-lived. (See Simpson, page 16)

Specifically, Simpson teaches a GABA receptor agonist used in a clinical trial with dismal results; tinnitus sufferers showed that the GABA receptor agonist was only slightly better than placebo while the occurrence of very severe side effects. (See Simpson, page 16) Another anticonvulsant yielded more positive results for treating tinnitus, however, only among patients with "cochlear-synaptic" tinnitus and not among general tinnitus sufferers. (See Simpson, page 16) Furthermore, Simpson concludes with a statement that "no pharmaceutical agent other than lignocaine has been shown to relieve tinnitus". (See Simpson, page 17) Simpson explains that the lack of adequate treatments for tinnitus is largely attributed to a lack of knowledge as to the physiological processes giving rise to tinnitus.

Analysis for obviousness must consider the subject matter as a whole to ascertain if it would have been obvious at the time the invention was made. When considering the subject matter as a whole at the time the invention was made, it is evident that the references cited by the Examiner do not teach Applicant's invention

and would not lead a person skilled in the art to select compounds of Formula I, as taught by Applicant, for the treatment of tinnitus.

If a person of ordinary skill in the art sought a treatment for tinnitus, that person would not have chosen the compounds taught by Applicant. Specifically, as disclosed in the references cited by the Examiner, all prior known uses of carbamazepine derivatives at the time of the invention were for the treatment of epilepsy. While the Examiner has attempted to qualify tinnitus as a form of "epilepsy", it is not. Simpson expressly teaches that tinnitus has its origin in numerous other conditions and that there is a lack of knowledge as to the physiological processes that give rise to tinnitus. (See Simpson, page 12.) Moreover, as discussed above, Simpson highlights the lack of effectiveness of anticonvulsants for the treatment of tinnitus. Thus, one skilled in the art at the time of the invention would not prepare compounds of Formula I, as taught by Applicant, and test the compounds for properties and purposes separate from their utility in treating epilepsy.

Applicant further posits that the nature of the problem to be solved would not lead a person of ordinary skill in the art at the time the invention was made to look at the references in a manner suggested by the Examiner. Applicant claims a method of treating tinnitus, however, references cited by the Examiner do not address the problem of treating tinnitus. Rather, Volosov teaches a controlled-release delivery system using low-melting wax to improve bioavailability of drugs, with absolutely no mention of tinnitus. Meanwhile, Benes teaches improved formulations of oxcarbazepine and derivatives to treat epilepsy, to overcome the low efficacy and bioavailability of known anticonvulsants. The additional reference of Simpson would only lead one skilled in the art further away from combining the references because it emphasizes the unknown nature of tinnitus and the many (prior) unsuccessful treatments for the disorder.

A determination of obviousness rests on underlying issues of fact articulated by the Graham factors. The Graham test for obviousness, however, fails when applied to the present application. First, as discussed above in distinguishing the references, the scope and content of the prior art does not establish all of the claim limitations of Applicant's Claim 7 in the references cited by the Examiner. Second, the differences between Applicant's claimed invention and the teachings of the references cited by the

Examiner are so great, as evidenced by the vast differences in the nature of the problem to be solved, that one skilled in the art at the time of the invention would not have combined the references to arrive at Applicant's Claim 7.

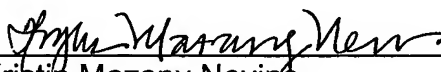
Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of Claims 7 and 9 – 13 under 35 U.S.C. § 103(a).

**II. Conclusion**

In view of the foregoing, Claims 7, 9 – 13 are in condition for allowance, and Applicant earnestly solicits a Notice of Allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this Application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration to this Amendment and Reply is respectfully requested.

Respectfully submitted,  
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